REMARKS

Rejections Under 35 U.S.C. § 103(a)

Claims 1-5, 8-11, 15/1, 15/2, 15/3, 15/4, 15/5, 15/8, 15/9, 15/10, and 15/11 were rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 5,514,378 to Mikos ("Mikos") in view of U.S. Patent No. 3,514,791 to Sparks ("Sparks") or U.S. Patent No. 4,795,459 to Jauregui ("Jauregui"). Claims 12-14, 15/12, 15/13, and 15/14 were rejected as obvious over Mikos in view of Sparks or Jauregui and further in view of U. S. Patent No. 5.709,854 to Griffith-Cima, et al. ("Griffith"). Claims 1-5 and 8-15 were rejected as obvious over Sparks in view of Mikos or Griffith and in view of either Jauregui or U. S. Patent No. 4,916,193 to Tang, et al. ("Tang"). Applicants respectfully traverse these rejections.

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications

that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992); *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The standard for obviousness under 35 U.S.C. 103 was recently reaffirmed by the U.S. Supreme Court in KSR Int'l. Co. v. Teleflex, Inc. 2007 U.S. LEXIS 4745; 75 U.S.L.W. 4289.

According to the Supreme Court,

"often it will be necessary ... to look to interrelated teachings of multiple patents; the effects of demands known to design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit.

In response to this decision, on May 3, 2007, the Assistant Commissioner of the U.S. Patent Office Margaret Facarino sent to the Technology Center Directors a memo, stating in relevant part:

(1). The court reaffirmed the *Graham* factors in the determination of obviousness under 35 U.S.C §103(a). The four factual inquiries under *Graham* are:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims at issue;

(c) resolving the level of one of ordinary skill in the art; and

(d) evaluating evidence of secondary consideration.

Graham v. John Deere, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966)

(2) The court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. §103(a).

(3) The court rejected the rigid application of the "teaching, suggestion or motivation" (TSM) test, which required a showing of some teaching, suggestion or motivation in the prior art that would lead one of ordinary skill in the art to combine the prior art elements in the manner claimed in the application or patent before holding the claimed subject matter obvious.

(4) The court noted that the analysis supporting a rejection under 35 U.S.C §103(a) should be made explicit, and it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant art to combine the [prior art] elements" in the manner claimed.

"Therefore, in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed."

The Scope and Content of the Prior Art

The prior art cited by the examiner fails to disclose or provide:

(1) each claimed element, specifically forming the matrix in the shape of a cell-matrix construct comprising a fibrous matrix in the shape of a heart valve or heart valve leaflet.

(2) a reasonable expectation that if one did provide such a matrix, that the cells would attach to and proliferate within the matrix to form a **functional** structure. This is further demonstrated

by the enclosed excerpt from Wikipedia on heart valves. Applicants are claiming a biological heart valve.

Mikos

Mikos discloses biocompatible porous polymer membranes prepared by dispersing salt particles in a biocompatible polymer solution. Mikos discloses that a three dimensional structure can be manufactured from the membranes. The resulting three-dimensional foam or shape is a porous, biocompatible matrix to which cultured cells can attach and proliferate, and can be used for organ transplant or reconstructive surgery (Mikos, column 3, lines 25-45).

Mikos discloses matrices having a particular shape; not function. There is no disclosure that one can form a structure that can move and function as the structure to be replaced, such as a heart. A cartilaginous structure is not functional other than as a support structure. Cartilage does not move repeatedly. It is a hard ***avascular*** support structure. In contrast, a heart valve must move repeatedly, be elastic and flexible, and withstand enormous strain.

Sparks

Sparks describes a die into which is placed a Dacron mesh secured to a stainless steel supporting ring (see column 5, lines 18-24). The die consists of a tube and mandrel (col. 3, lines 29-31). The die may be seeded with cells to make special parts, periosteal cells being used to make bone and epithelial cells being used to make epithelial tissue (abstract). Figures 6-12 illustrate a die for growing a tricuspid heart valve. Sparks further discloses that natural body processes produce the necessary connective tissue to fill the die cavity and form the valve graft (see column 2, lines 27-32 and column 5, lines 32-36).

Sparks is similar to Mikos in that it provides only a stationary support structure, but fails to provide a structure that can also function as a heart or heart valve when seeded with cells. It is

also clearly different in not forming a matrix into which cells are seeded and proliferate, but rather that any cells on sit on the surface of the mesh.

Griffith

Griffith discloses a cell-polymeric solution which is injected into an animal where the polymer crosslinks to form a polymeric hydrogel containing dispersed cells and the cells form new tissue in the animal. The hydrogel solution containing the cells can be injected directly into a patient where it hardens into a matrix having cells dispersed therein, or the hydrogel is poured into a mold having a desired anatomical shape, then hardened, which can be implanted into a patient (Griffith, column 1, lines 42-61).

Griffiths cannot form a specific shape. Griffiths is a gel of amorphous shape. Griffiths forms a hydrogel, not a fibrous structure.

Jauregui

Jauregui discloses an implantable prosthetic device made of biocompatible polymer and having a substantially continuous layer of autologous living cells attached via oligosaccharide-lectin recognition linkages (abstract).

As previously noted, this also only discloses a material having cells seeded on the surface, not within a matrix that forms a functional structure.

Tang

Tang discloses totally or partially bioabsorbable devices capable of degrading into biologically innocuous components.

Analysis as to Level of Skill and Knowledge in the Art; Differences with the Art

There is a high level of skill in the field of tissue engineering, but at the time this application was originally filed, May 19, 1995, more than ten years ago, there had been little clinical reduction to practice and there was a great deal of unpredictability.

Claims 1-5, 8-11, 15/1, 15/2, 15/3, 15/4, 15/5, 15/8, 15/9, 15/10, and 15/11 are not obvious over Mikos in view Sparks or Jauregui.

The claims define a method of making a cell-matrix construct for use as a heart valve or heart leaflet comprising implanting into an animal a cell-matrix construct comprising

a fibrous matrix in the shape of a heart valve or heart valve leaflet.

wherein the matrix is formed of a biocompatible, biodegradable polymer

having seeded therein cells selected from the group consisting of endothelial cell, myfibroblasts, skeletal, vascular smooth muscle cells, myocytes, fibromyoblasts and ectodermal cells,

wherein the cell-matrix construct can withstand repeated stress and strain.

Mikos does not disclose a method for making a cell-matrix construct for use as a heart valve, let alone a method that involves the steps recited in claim 1. Mikos does not disclose a method that results in a heart valve that can resist repeated stress and strain as recited in claim 1. None of Sparks or Jauregui make up for these deficiencies.

The Examiner has cited to Mikos, column 2 lines 15+, citing to a disclosure by Vacanti, et al, 1988, that the scaffold should mimic the natural tissue counterpart, and that the scaffold should serve as both a physical and adhesive support for isolated cells during culturing thereof, attaching the relevant portion of Mikos (Mikos column 2, lines 16-44). Applicants suppose that the Examiner is using this disclosure in Mikos as a disclosure of the limitation in claim 1, that the method comprises implanting into an animal a cell-matrix construct, comprising a fibrous matrix shaped into a heart valve or heart valve leaflet.

Vacanti, et al., *J. Pediatric Surgery* 23(1):3-9 (1988) ("Vacanti 1", a copy of which is attached) discloses cell transplantation by a method which includes attaching cell preparations to bioerodible artificial polymers in cell culture, and then implanting this polymer-cell scaffold into

animals. Vacanti 1 discloses a method that allows implantation of large numbers of cells (see Vacanti 1, page 7, right column). Vacanti 1 does not disclose or suggest how implanted matrices can be made to withstand stress and strain. Indeed, Vacanti only discloses seeding of cells onto fibrous materials of amorphous shape, which are culture *in vitro*, then implanted. This is supported by a lecture presented by the same author (Vacanti, Beyond *Transplantation*, 123:5459 (1988) ("Vacanti 2", a copy of which is attached), cited by Mikos in the column to which the Examiner referred. Vacanti 2 discussed strides made in cell transplantation, much of the discussion including results from the studies in Vacanti 1. However, Vacanti 2 noted (on page 549, right column), that much work needed to be done, but the hope was that some day cellular chimeras would provide replacement tissue for patients as an alternative to organ transplantation as currently practiced.

As admitted by the Examiner, Mikos is silent about vascular tissue. However, the Examiner asserted that the use of tissue engineering employing both resorbable and nonresorbable polymer scaffolds to replace diseased tissue, including vascular tissue, is known in the art, citing Sparks and Jauregui, and that these polymers can be molded to mimic the shape of the tissue to be engineered is also known in the art (*See* Mikos, col. 13+ cited by the Examiner). That the technology and necessary polymers are known may be true, however, making a structure with the requisite mechanical physical and mechanical properties necessary for biological function, especially a structure such as a heart valve, has been a challenge and was neither disclosed by nor predicted at the time this application was filed. Claim 1 requires the cell-matrix be able to withstand repeated stress and strain. This is a critical limitation of a claim to a construct which is to be used to replace a heart valve or heart leaflet, structure which must open and close hundreds of times every hour, thousands of times every day, for years. Mikos is silent about heart valves, and therefore does not disclose or suggest how to make valves which

can withstand repeated stress and strain. None of Sparks or Jauregui make up for this deficiency. Therefore the claims are non-obvious over Mikos in view of Sparks and Jauregui.

Claims 12-14, 15/12, 15/13, and 15/14 are non-obvious over Mikos in view of Sparks or Jauregui and further in view of Griffith.

Claims 12-15 define a method for making a cell-matrix construct for use as a heart valve, with the limitations recited in claim 1. As discussed above, Mikos does not disclose all the elements of claim 1; none of Sparks or Jauregui to not make up for this deficiency. Similarly, Griffith does not make up for the efficiencies in Mikos. Therefore, the claims are non-obvious over the cited art.

Claims 1-8 and 8-15 are not obvious over Sparks in view of Mikos or Griffith-Cima and in view of either Jauregui or Tang.

The references cited by the Examiner do not disclose all of the claim limitations. Sparks does not disclose a method for making cell-matrix constructs for use as a heart valve as defined by claim 1. Sparks does not disclose or suggest using a fibrous polymeric matrix in the shape of a heart valve or heart valve leaflet which is implantable. Sparks does not disclose how to make a cell-matrix construct which can withstand repeated stress and strain. None of the secondary references make up for these deficiencies.

Sparks discloses a stainless steel die for growing a heart valve. A die cavity is formed between the outer and inner die members, and it is in this die cavity that the heart valve is grown (see Sparks, column 5, lines 18-20). A mesh reinforcing member is placed in the cavity, and connective tissue entering the die cavity through perforations in the outer die member encapsulates the mesh and completely fills the die cavity to form a heart valve which is similar in shape to the mesh. Thus the graft has a rigid circular base rim containing a steel ring (Sparks, column 5, lines 32-40). It is clear from the disclosure in Sparks, that the method of forming the

graft involves implanting a stainless steel die in an animal, containing Dacron mesh for reinforcement. Sparks does not teach that the fibrous matrix must be in the shape of a heart valve or heart leaflet. It is not clear how this can be accomplished using a Dacron mesh fitted in the space between the die members 40 and 42, shown in figure 7 of Sparks as 51. The Examiner's attention is respectfully drawn to the claim language, which recites "a method of making a cell-matrix construct for use as a heart valve, comprising implanting into an animal a cell-matrix construct comprising a fibrous matrix in the shape of a heart valve or heart valve leaflet". Contrary to the Examiners' assertion, Sparks does not disclose a method for making a cell-matrix construct for use as a heart valve that involves implanting into an animal a fibrous matrix formed of a polymer matrix that has been seeded with specific selected cells. The Examiner cannot separate the features disclosed in Sparks. The reference must be considered as a whole. Sparks discloses a method of forming a heart valve graft that involves implanting a perforated stainless steel die made up of two members (40 and 42), separated by a cavity within which the valve graft is formed by connective tissue entering the die cavity. This is in fact claimed in Sparks. The stainless steel die is essential to form the three dimensional structure of the heart valve (please see the Sparks, Figures 6-12). Furthermore, Dacron mesh is not biodegradable, a characteristic required by claim 1.

With respect to cell seeding, Sparks discloses that when a graft of epithelial tissue is desired, the die may be seeded with epithelial cells (column 4, lines 3-10). Sparks also states that before implanting a bone graft die, it is seeded with periosteal cells (column 4, lines 50-60). Further, Sparks does not disclose seeding any cells in valve grafts. Sparks is very clear when cell seeding is required. Sparks is silent about seeding cells in valve grafts. Therefore, a *prima facie* case of obviousness has not been established, since the references (when combined) do not teach or suggest all the claim limitations.

There is no similarity whatsoever between the two methods. The only similarity between Sparks and the claims is the name of the resultant product. There is no similarity in the process of making, or the materials used, therefore it is expected that there would be no similar physical properties.

The Examiner has cited to Mikos, alleging a disclosure by Vacanti 1, that the scaffold should mimic the natural tissue counterpart, and that Vacanti, et al. provides evidence that better results are obtained when the matrix is first implanted, prevascularized and then seeded with select cell, attaching the relevant portion of Mikos (Mikos column 2, lines 16-44). It is not clear what Mikos means by "better results" cited by the Examiner; however, since Mikos is referring to Vacanti, the "better results" obtained are not concerned with a graft that can withstand repeated stress and strain, since Vacanti is only concerned with enhancing viability of large numbers of transplanted cells seeded onto an amorphous fibrous support structure (a gauze). It is clear from the discussion in Vacanti 1 and Vacanti 2 (discussed above), that Vacanti 1 cannot make obvious the claimed method, which provides heart valves which can withstand repeated stress and strain. Vacanti does not recognize the problem with somehow providing the cell matrix with mechanical properties such as strength, flexibility, resistance to strain – features essential for a structure which will be opened, closed, and subjected to pressures every second, every hour, every day, every month, every year in the individual's life following implantation. There are simply no comparable requirements when it comes to a parenchymal tissue such as a liver or pancreas.

The Examiner also asserted that the materials used by Applicants are well known and known equivalents are taught by Jauregui or Tang, stating that Tang teaches that bioresorbable materials play a critical role in fabrication of devices used for tissue regeneration. The issue here is not merely using biodegradable materials to make heart valves. That biodegradable materials

can be used in tissue engineering is known in the art, as correctly stated by the Examiner. It is also known that these polymers can be molded to mimic the shape of the tissue to be engineered. However, making a structure with the requisite mechanical physical and mechanical properties necessary for biological function has been the challenge.

The claims do not merely define a method that can be accomplished by substituting the Dacron Mesh in the stainless steel die of Sparks, with the biodegradable materials disclosed in Jauregui or Tang, or the use of the materials disclosed in Jauregui or Tang shaped into a three dimensional structure as suggested by Griffith and or Mikos. Claim 1 requires the cell-matrix be able to withstand repeated stress and strain. This is a critical limitation of a claim to a construct which is to be used to replace a heart valve or heart leaflet, structure which must open and close hundreds of times every hour, thousands of times every day, for years.

According to the Examiner's assertion, the device of Sparks as modified would inherently possess the properties that would be capable of withstanding cyclic stresses and strains, since the valve is designed to function as a replacement of a natural valve. Sparks does not disclose biodegradable biocompatible materials which provide these properties. Sparks instead teaches the use of non-biodegradable materials for making such a structure. Since this is not a fully biodegradable device, the device is not the same as what is claimed. It cannot be an inherent disclosure; the elements are explicitly different.

The Examiner must provide a technical reason for a conclusion of inherency. According to the MPEP §2112 "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d

1949, 1950-51 (Fed. Cir. 1999) (citations omitted)". As demonstrated by Shinoka, et al. *Circulation*, 94(9 Suppl):II164-8 (1996) ("Shinoka 1", abstract attached), the property of withstanding stress and strain is not inherent in biodegradable polymers, therefore a mere disclosure that a biodegradable polymer can be used for tissue engineering cannot make obvious the claimed method and cell-construct. Moreover, it is not clear to the Applicants what modification the Examiner is referring to. If the Examiner is referring to the Dacron mesh, there is no disclosure in Sparks or any reason for a skilled artisan to conclude from Sparks, that the Dacron mesh seeded with cells with have the necessary strength and flexibility and be able to withstand repeated stress and strain. None of the cited references disclose that the biodegradable polymers necessarily possess the ability to withstand repeated stress and strain or how to adapt these polymers to have the requisite property. In fact, Shinoka 1 demonstrates this point.

There is no motivation to combine these references as the Examiner has done, nor would one skilled in the art have a reasonable expectation of success if one did so, based on the art, to yield a structure which can withstand repeated stress and strain. For example, Sparks describes dies containing stainless steel, screws, and plates (see column 5, lines 18-31). This is completely different from the formation of tissue by injecting a cell-polymeric **solution** that gels *in vivo* (Griffith). As stated by the Examiner, Griffith teaches that the degradable template may be shaped or formed prior to implantation into the patient, and as such a combination of Griffith with Sparks would be impossible. Sparks needs the die to be implanted in order to shape the heart valve, Griffith teaches the implantation of a degradable hydrogel template with essentially no defined shape or structure and minimal mechanical properties. Not only is there no motivation to combine, there would be no reasonable expectation of success if one did so.

Mikos discloses preparing biocompatible porous polymer membranes by dispersing particles in a biocompatible polymer solution. There would be no motivation for one of ordinary

skill in the art to replace the Dacron mesh with an absorbable matrix as taught by Mikos or Griffith, nor would one have a reasonable expectation that one could make a strong, flexible structure that could function has a heart valve or leaflet.

Jauregui discloses growing cells *on* a device that is to be implanted. Jauregui does not disclose seeding cells into a fibrous cell structure which is eventually replaced by the cells. Jauregui does not lead one skilled in the art to make a construct that is strong, flexible and useful as a heart valve. A skilled artisan would not be motivated to combine Jauregui and Sparks to arrive at the claimed method and construct, much less have a reasonable expectation of success. According to the MPEP §2143.01 "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the **desirability** of the combination".

Sparks does not disclose or suggest a method of making a cell-matrix construct for use as a heart valve comprising implanting into an animal a cell-matrix construct as recited in claim 1, which is first cultured at a first site in a patient prior to being transplanted to a second site (claim 3). None of Mikos or Griffith or Jauregui makes up for this deficiency.

With respect to claim 8, claim 8 is dependent on claim 1, and recites the added limitation that the heart valve has mechanical strength, and flexibility or pliability. As already disclosed, Sparks does not disclose a method of making a heart valve as recited in claim 1, such that the valve has mechanical strength and flexibility or pliability. The Examiner asserts that the newly formed heart tissue would inherently possess the strength, flexibility and/or pliability of the tissue it is to replace. The Examiner has provided no technical reasoning for this conclusion and the literature rebuts such a conclusion. Without such a disclosure in Sparks, it would appear that the Examiner is concluding that because the graft is intended to replace heart valve, it would have all the characteristics of a heart valve. Please see Shinoka, et al. *Ann Thorac Surg.*, 60(6

Suppl):S513-6 (1995) ("Shinoka 2", a copy of abstract attached) which discussed the disadvantages of valve replacements using other materials such as bioprosthetics or mechanical valves. Clearly, the mere fact that an object is intended to replace a biological structure does not inherently confer to it the properties of that structure.

Conclusion

The art cited by the Examiner does not, either alone or in combination, recite all the elements of the claims as required by a rejection under 35 U.S.C 103(a). Even if they did, as the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. The Examiner has provided no reasoning why a person of ordinary skill in the art would combine the references as the Examiner has done. Therefore, the claims are non-obvious over the prior art.

Allowance of claims 1-5 and 8-15, is respectfully solicited.

Respectfully submitted,

/Patrea L. Pabst/
Patrea L. Pabst
Reg. No. 31,284

Date: May 8, 2007
PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2151
(404) 879-2160 (Facsimile)